

1-Triflylpyrroles as efficient dienophiles in normal electron demand [4+2] cycloaddition reactions under pressure†

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1-Triflylpyrroles bearing acetyl group(s) on position 3, or 2 and 4, are efficient dienophiles in normal electron demand Diels–Alder reactions activated by high pressures and Lewis acids.

In spite of its age, the [4+2] cycloaddition process between a diene and a dienophile remains one of the most attractive and selective chemical transformations for the construction of (poly)cycles.¹ Perhaps because of the aromatic stabilization of pyrrole **1**, there are very few reports of pyrrole derivatives acting as dienophile in inverse electron-demand cycloaddition reactions (Fig. 1).² In many intermolecular cases, yields were at best modest, and, expectedly, raised when the intramolecular variant was carried out. The only report on the possible involvement of pyrrole as dienophile in *normal* electron-demand [4+2] processes was published fifteen years ago.³ Thus, *N*-benzenesulfonylpyrrole **2**, bearing an acetyl group on carbon 3 of the heterocycle, was found to react with isoprene to deliver the expected cycloadducts **3** as a 1 : 2 regioisomeric mixture. The merit of such a transformation lies mainly in the fact that, in the case of a carbon-centered electron withdrawing substituent, the produced quaternary center on position 3 keeps the product from recovering aromaticity. However, harsh conditions (195 °C, 72 h) had to be used, conversion was not complete (34%) and isolated yields were low (17%), a reflection of the strong aromatic character of the substrate. This forbade the practical development of the synthetic approach and its use in the total synthesis of natural and unnatural products encompassing a 5-membered nitrogenous heterocycle (*e.g.* tazettine **4**). This result nevertheless pointed out the feasibility of such a reaction.

High pressures have been shown to constitute a powerful activation method of Diels–Alder processes, especially when conducted in the presence of a Lewis acid.⁴ However, reacting 1-tosyl-3-acetylpyrrole (**5a**) and zinc chloride (0.1 equiv.) with either 2,3-dimethylbuta-1,3-diene (DMB) (**6**) or cyclohexa-1,3-diene (**7**) under 12 kbar led to insufficient results (Table 1, entries 1 and 2).

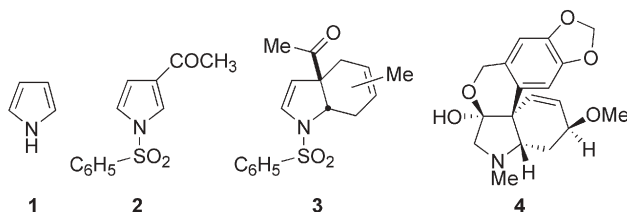


Fig. 1 Structures of pyrroles **1–2**, of cycloadduct **3** and of tazettine **4**.

† Electronic Supplementary Information (ESI) available: General information, procedures and copies of NMR spectra. See <http://www.rsc.org/suppdata/cc/b4/b414978e/>

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Interestingly, the major diastereomer produced in the case of diene **7** is the one defined as *exo*, *i.e.* corresponding to the smaller steric hindrance generated by the acetyl group (when compared to the *N*-sulfonyl heterocycle) in the transition state.⁵

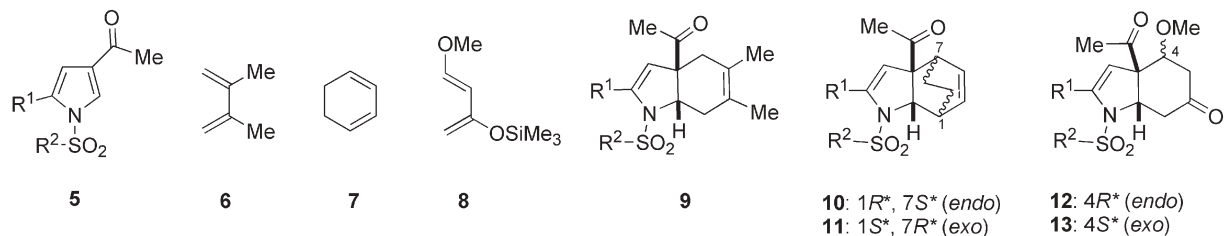
On the assumption of poorly reactive pyrrole requiring more than two electron withdrawing groups to generate a usable cycloaddition process, it was decided to study the dienophilic behavior of a pyrrole trisubstituted on positions 1, 2 and 4.⁶ Indeed, the documented interaction between 2,4-biscarbomethoxyfuran and Danishefsky's diene **8** was shown to involve the 4,5 carbon–carbon double bond in a complete regioselective fashion.⁷

Thus the known and easily accessible 2,4-diacetyl-1-*p*-tosylpyrrole (**5b**) was singled out as the best available candidate to pursue the present study.^{8,9} Thermal conditions in the presence of the same Lewis acid led to disappointing results and the desired cycloadduct **9b** was isolated in low yield (entry 3). However, complete site selectivity and chemoselectivity were observed as no other alternate cycloadduct or bisadduct could be detected. Conducting the reaction under a pressure of 12 kbar, at 50 °C and in the presence of one full equivalent of the same Lewis acid led to an optimised yield of 48% (entry 4). The use of cyclohexa-1,3-diene (**7**) led to essentially the same result, the expected cycloadducts **10b** and **11b** being isolated only in moderate yield (entry 5).

Replacing the *p*-tosyl group with a trifluoromethylsulfonyl (triflyl) unit, a more powerful activating group, resulted in a dramatic increase of reactivity of the pyrrolyl carbon–carbon double bond.¹⁰ Thus, placing 3-acetyl-1-triflylpyrrole (**5c**) and dimethylbutadiene **6** under a pressure of 12 kbar and in the presence of 10% mol ZnCl₂ led only to a 31% conversion after 36 h; the conversion became however nearly quantitative when the same reaction was carried out under 16 kbar (entry 6).¹¹ The desired cycloadduct **9c** was then isolated in a gratifying 80% yield. A complete conversion was also obtained with cyclohexa-1,3-diene (**7**) and a 13 : 87 mixture of *endo/exo* cycloadducts **10c** and **11c** were isolated in 49% yield (entry 7).¹³

The positive impact of the triflyl substituent on the reactivity of pyrrole derivatives was next studied on 2,4-diacetylpyrrole (**14**).¹⁴ The thermal reaction between **5d** and diene **6** (130 °C) in the presence of ZnCl₂ led to degradation of the material, indicative of the sensitivity of the substrate. Activation by high pressures proved once more to be valuable. Compressing a methylene chloride solution of **5d** and 6 equivalents of DMB at 50 °C for 72 h in the presence of ZnCl₂ led to a complete conversion and a regioselective formation of adduct **9d**, which was isolated in 80% yield (entry 8). The beneficial effect of the triflyl group is once again illustrated

Table 1 Cycloaddition reactions between pyrroles **5** and dienes **6–8**



Entry	Pyrrole	R ¹	R ²	Diene (equiv.)	P/kbar	T/°C ^a	cat. ^b	t/h	Conv. ^c (%)	Product	endo/exo	Yield (%)
1	5a	H	<i>p</i> -C ₆ H ₄	6 (6)	12	50	ZnCl ₂	36	Traces	9a	—	— ^d
2	5a	H	<i>p</i> -C ₆ H ₄	7 (6)	16	50	ZnCl ₂	36	50	10a/11a	5 : 95	25
3	5b	Ac	<i>p</i> -C ₆ H ₄	6 (12)	10 ⁻³	130	ZnCl ₂	168	38	9b	—	19
4	5b	Ac	<i>p</i> -C ₆ H ₄	6 (6)	12	50	ZnCl ₂ ^e	72	59	9b	—	48
5	5b	Ac	<i>p</i> -C ₆ H ₄	7 (6)	16	50	ZnCl ₂	36	44	10b/11b	7/93	31
6	5c	H	CF ₃	6 (6)	16	50	ZnCl ₂	36	91	9c	—	80
7	5c	H	CF ₃	7 (6)	16	50	ZnCl ₂	36	97	10c/11c	13 : 87	49
8	5d	Ac	CF ₃	6 (6)	12	50	ZnCl ₂	36	100	9d	—	80
9	5d	Ac	CF ₃	7 (6)	16	50	ZnCl ₂	36	100	10d/11d	35 : 65	70
10	5d	Ac	CF ₃	8 (6)	16	50	EuFOD	72	80	12a/13a ^f	60 : 40	61

^a CH₂Cl₂ is used as solvent, except in entry 3 (toluene). ^b Unless otherwise indicated, 0.1 equiv. of catalyst was used. ^c Conversion. ^d Not isolated. ^e One equivalent of catalyst was used. ^f Isolated after hydrolysis of the silyl enol ether group present in the cycloadducts.

from the reaction with cyclohexa-1,3-diene (**7**). Optimised conditions led to a complete conversion and furnished a 70% isolated yield of a 35 : 65 mixture of *endo* and *exo* stereoisomers (**10d** and **11d**, respectively, entry 9). Again, the *exo* diastereomer proved to be the major one. Interaction with the electronically activated diene **8** resulted in an 80% conversion after 72 h under 16 kbar (entry 10). The products proved to be a 6 : 4 diastereomeric mixture of the expected *endo* and *exo* adducts (61% isolated yield). Thus the triflyl group plays a significant role on the course of the reaction by allowing the desired transformation to occur in a very regioselective and efficient manner. Pivotal to the synthetic utility of this approach is the ability to remove the triflyl group.¹⁵ Thus, for instance, simple treatment of cycloadduct **9d** with sodium methanolate not only cleaved the triflamide, but also diastereoselectively introduced a new functional group in the form of an ether, delivering **15** in 61% isolated yield (Fig. 2).

In summary, pyrroles bearing one or two electron withdrawing substituents (on position 3 or on positions 2 and 4, respectively) can be used as good dienophiles in normal electron demand cycloadditions on the condition that they bear a triflyl group on position 1. A combination of high pressures and a Lewis acid allows the reaction to proceed efficiently under mild thermal conditions. The door is now open to the use of this methodology in the total synthesis of natural and unnatural products, as well as in the production of new scaffolds for the preparation of libraries.

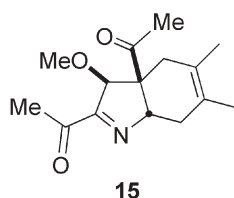


Fig. 2 Structure of compound **15**.

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Notes and references

- For general reviews, see: (a) W. Oppolzer, Combining C–C π bonds, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon Press, Oxford, UK, 1991, vol. 5, ch 4.1; (b) F. Fringuelli and A. Taticchi, *The Diels–Alder Reaction*, John Wiley & Sons, Chichester, UK, 2002; (c) E. J. Corey, *Angew. Chem. Int. Ed.*, 2002, **41**, 1650; (d) K. C. Nicolaou, S. C. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, 2002, **41**, 1668.
- (a) G. Seitz and T. Kämpchen, *Arch. Pharm.*, 1978, **311**, 728; (b) R. L. Cobb, V. C. Vives and J. E. Mahan, *J. Org. Chem.*, 1978, **43**, 931; (c) J.-H. Li and J. K. Snyder, *J. Org. Chem.*, 1993, **58**, 516; (d) M. F. Hsieh, R. K. Peddinti and C.-C. Liao, *Tetrahedron Lett.*, 2001, **42**, 5481; (e) Z.-X. Yu, Q. Dang and Y.-D. Wu, *J. Org. Chem.*, 2001, **66**, 6029; (f) C.-C. Liao and R. K. Peddinti, *Acc. Chem. Res.*, 2002, **35**, 856; (g) Q. Dang and J. E. Gomez-Galeno, *J. Org. Chem.*, 2002, **67**, 8703; (h) D. Giomi and M. Cecchi, *Tetrahedron*, 2002, **58**, 8067; (i) B. R. Lahue, S.-M. Lo, Z.-K. Wan, G. H. C. Woo and J. K. Snyder, *J. Org. Chem.*, 2004, **69**, 7171.
- E. Wenkert, P. D. R. Moeller and S. R. Piettre, *J. Am. Chem. Soc.*, 1988, **110**, 7188.
- (a) N. Isaacs, *Tetrahedron*, 1991, **47**, 8463; (b) F.-G. Klaerner, M. K. Diedrich and A. E. Wigger, *Chemistry under Extreme or Non-Classical Conditions*, ed. R. Van Eldick and C. D. Hubbard, John Wiley and Sons, New York, 1997, pp. 103–161; (c) J. Jurczak and D. T. Gryko, *Chemistry under Extreme or Non-Classical Conditions*, ed. R. Van Eldick and C. D. Hubbard, John Wiley and Sons, New York, 1997, pp. 163–188; (d) I. Chataigner, E. Hess, L. Toupet and S. R. Piettre, *Org. Lett.*, 2001, **3**, 515; (e) A. Chrétien, I. Chataigner, N. L’hélias and S. R. Piettre, *J. Org. Chem.*, 2003, **68**, 7990.
- The stereochemistry of the diastereomers was ascertained with the help of NOESY NMR experiments. *Endo* addition can be defined as “that

- particular arrangement of reactants in which the more bulky side of the diene is under the more bulky side of the dienophile”, meaning the pyrrole part in this case.^{1b} In this precise case, the volume of the transition state leading to the *exo* diastereomer is probably more compact than the one delivering the *endo* cycloadduct.
- 6 The choice of the 2,4 disubstitution was dictated by the nearly complete lack of reactivity of electron-poor five-membered heterocycles bearing an electron withdrawing group on carbon 2: this was expected to translate into a site selectivity on the heterocycle, see: ref. 3.
 - 7 E. Wenkert and S. R. Piettre, *J. Org. Chem.*, 1988, **53**, 5850.
 - 8 2,4-Diacetylpyrrole was prepared by a sequential, double Friedel–Crafts reaction on pyrrole, according to the published procedures, see: (a) S. Cadamuro, L. Degani, S. Dughera, R. Fochi, A. Gatti and L. Piscopo, *J. Chem. Soc.*, 1993, 273; (b) D. O. Alonso, G. Buldain and B. Frydman, *J. Org. Chem.*, 1984, **49**, 2619.
 - 9 2,4-Diacetylpyrrole was tosylated according to literature procedure, see: T. Masquelin, E. Broger, K. Müller, R. Schmid and D. Obrecht, *Helv. Chim. Acta*, 1994, **77**, 1395.
 - 10 Analogous reactions conducted with indole derivatives have shown the beneficial effect of the triflyl group (with regards to the tosyl substituent), allowing the desired transformation to reach completion under milder conditions and in shorter times. I. Chataigner and S. R. Piettre, unpublished results.
 - 11 Triflated pyrrole **5c** was prepared by interacting 3-acetylpyrrole¹² with triflic anhydride in the presence of *N,N*-diisopropyl-*N*-ethylamine at $-78\text{ }^{\circ}\text{C}$ (79% isolated yield), according to the literature procedure, see: A. D. Abell, B. K. Nabbs and A. R. Battersby, *J. Am. Chem. Soc.*, 1998, **120**, 1741.
 - 12 M. Kakushima, P. Hamel, R. Frenette and J. Rokach, *J. Org. Chem.*, 1983, **48**, 3214.
 - 13 Competitive polymerisation of the diene resulted in the formation of a gummy material, trapping some of the product.
 - 14 Pyrrolyl substrate **5d** was easily prepared by reacting **14** with *N,N*-bistriflylphenylimide (78% isolated yield). See: J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, 1973, 4607.
 - 15 Sulfonamides have been reported to be efficiently deprotected either under nucleophilic conditions or through the action of a reductant, see: (a) J. B. Hendrickson and R. J. Bergeron, *Tetrahedron Lett.*, 1973, 3839; (b) A. Satake, H. Ishii, I. Shimizu, Y. Inoue, H. Hasegawa and A. Yamamoto, *Tetrahedron*, 1995, **51**, 5331; (c) V. Hilarius, H. Buchholz, P. Sartori, N. Ignatiev, A. Kucherina and S. Datsenko, *PCT Int. Appl.*, 2000, 2000046180.